



Trade Science Inc.

# Organic CHEMISTRY

An Indian Journal

Full Paper

OCAIJ, 4(1), 2008 [50-53]

## Microwave accelerated green synthesis of dihydropyrimidinones

Mridula Phukan, Parthapratim Chaliha, Kalyan Jyoti Borah, Ashim Jyoti Thakur, Ruli Borah\*

Chemical Sciences Department, Tezpur University, Napaam-784028, Tezpur-Assam, (INDIA)

Tel.: +91 3712 267007/8/9 ; Fax: +91 3712 267005/6

E-mail : ruli@tezu.ernet.in

Received: 14<sup>th</sup> September, 2007 ; Accepted: 19<sup>th</sup> September, 2007

### ABSTRACT

The effect of microwave irradiation (MWI) was investigated for Biginelli reaction of aromatic aldehyde,  $\beta$ -ketoester, and (thio) urea without using organic solvent or catalyst under different microwave power level to the corresponding dihydropyrimidinones. These studies developed an improved microwave-assisted method for the synthesis of dihydropyrimidinones in green condition with good yields.

© 2008 Trade Science Inc. -INDIA

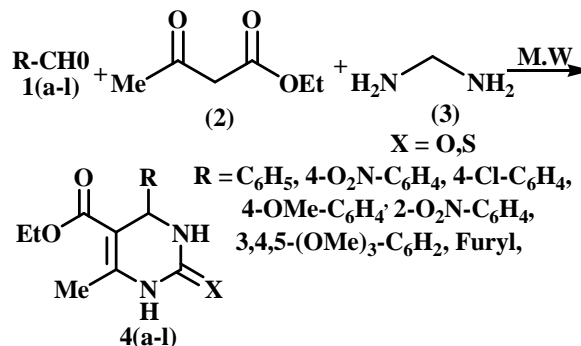
### KEYWORDS

Biginelli reaction;  
Dihydropyrimidine-  
2(1H)-ones;  
Microwave irradiation  
(MWD);  
Green synthesis.

### INTRODUCTION

The use of microwave irradiation in organic synthesis<sup>[1a-b]</sup> as non-conventional energy has gained more importance in terms of shorter reaction time, higher yields, and cleaner reaction. In addition, MWI increases the selectivity of some organic reaction under solventless condition. Sometimes microwave irradiation can lead to less by-products and/or decomposition products with homogeneous reaction mixture because of uniform heating throughout the sample in compared to traditional heating systems. Kappe<sup>[1c]</sup> et al investigated a series of acid catalyst Biginelli reactions in polar solvent (ethanol) using MWI at atmospheric pressure and showed neither a rate increase nor an increase in yields when the temperature was identical with conventional thermal heating. But superheating of reaction mixture by MWI increases the rate or yield of reaction at atmospheric pressure in ethanol that is due to rapid evaporation of solvent ethanol from the reaction mixture in open system.

3,4-Dihydropyrimidin-2(1H)-ones (DHPM), named as Biginelli compounds are an important class of compounds in the fields of drugs and pharmaceuticals<sup>[2]</sup>. They are known to possess wide range of distinct biological activities<sup>[3]</sup> such as antitumor, anti-inflammatory, antibacterial, antiviral, antihypertensives effects and integral backbones of several calcium channel blockers of the nifedipine-type. The classical Biginelli synthesis (SCHEME 1) is a one-pot three component cyclocon



SCHEME 1

condensation reaction using  $\beta$ -ketoester with aldehyde (aromatic and aliphatic) and urea or thiourea in ethanolic solution containing catalytic amounts of acid<sup>[2,4]</sup>. The main drawbacks of this method are use of mineral acid as catalyst, more reaction time, severe reaction condition, and unsatisfactory yields. Consequently, several improved procedures have been developed including classical conditions with microwave irradiation<sup>[1c-5]</sup> and by using Lewis acids as well as by protic acids as catalysts<sup>[6]</sup> such as  $Mg(ClO_4)_2$ ,  $KAl(SO_4)_2 \cdot 12H_2O$ ,  $FeCl_3$ ,  $ZnCl_2$ ,  $CuCl_2$  and  $NiCl_2$ , Indium(III) halide,  $NH_4Cl$ ,  $H_3BO_3$ ,  $Mn(OAc)_3 \cdot 2H_2O$ , silica-sulfuric acid,  $Sr(OTf)_2$ ,  $In(OTf)_3$ ,  $SiO_2$ - $NaHSO_4$ ,  $NH_2SO_3H$ , lanthanide triflate, etc. Recently<sup>[7]</sup>, the use of ionic liquids, polymer-supported reagents has also been reported in Biginelli reaction. The requirement of stoichiometric amount of catalysts, possible environmental pollution from organic solvents (ethanol, toluene etc), longer reaction time (3h to 8h), unsatisfactory yields and non-recycling of catalysts are the common difficulties in several of these methods. However, this has been observed in many procedures that the employed catalysts aren't always practically environmentally benign. Consequently, this leads to a heavy environmental pollution in waste disposal processes. Ranu<sup>8</sup> *et al* reported an efficient solvent-less and catalyst free Biginelli reaction by stirring a mixture of neat reactants at 100-105°C for an hour and producing DHPMs in high yields. As far as advent of green chemistry is concerned, there is a need still exists for reinvestigate the effect of microwave on the three-component Biginelli reaction of  $\beta$ -ketoester, aldehyde and urea or thiourea in neat condition without any solvent and catalyst for the synthesis of DHPMs. Therefore, synthesis of these DHPM compounds in high yields with improved procedure is of much current importance. In this communication, a new green synthetic method of 3,4-Dihydropyrimidin-2(1H)-ones (DHPM) is reported under MWI without any solvent as well as catalyst.

## EXPERIMENTAL

### General procedure and materials

All products were reported and their physical and spectroscopic data were compared with those of au-

thentic sample. Mps were determined on a Buchi melting point apparatus, Mod. B-540 and are uncorrected. IR spectra were recorded on a Nicolet Instruments 410-FTIR Spectrophotometer as KBr pellets. <sup>1</sup>HNMR spectra were obtained on a Bruker AMX- 300MHz spectrometer. The elements analysis were performed on a Perkin-Elmer 20 analyzer. TLC analysis was monitored on chromatographic plate using silica gel (Merck, 60-120 mesh). All microwave reactions has been performed in a domestic microwave oven (Samsung C103FL). Acetoacetic ester, aldehydes, urea, thiourea were all commercial products and were used without purification.

### Synthesis of dihydropyrimidinone

Aryl aldehyde **1** (2mmol),  $\beta$ -ketoester **2** (2mmol), (thio)urea **3** (3mmol) were taken in a 100ml beaker and irradiated inside the cavity of a domestic MW oven (Samsung C103FL) in neat without any solvent or catalyst at specified power level (900/600/450/300/180W) and reaction period. After completion of the reaction, as indicated by TLC, the resulting reaction mixture was cooled with ice-cold water. The solid product was washed with cold water (20ml) to remove the excess of urea or thiourea and then filtered. The remaining solid material was recrystallized from ethyl acetate/n-hexane or ethanol to afford the pure products.

## RESULTS AND DISCUSSION

In a typical procedure, a mixture of the aromatic aldehyde **1** (2mmol),  $\beta$ -ketoester **2** (2mmol), urea or thiourea **3** (3mmol) was taken in a 100ml beaker and irradiated inside the cavity of a domestic MW oven (Samsung C103FL) in neat without any solvent or catalyst at specified power level (900/600/450/300/180W). In case of benzaldehyde, this new method yielded 98% product at 600W power within 5minutes of irradiation. Kappe<sup>[1c]</sup> *et al* observed that MWI of benzaldehyde in ethanol solution using HCl acid as catalyst yielded only 89% product during 5minutes at power 400W. In order to generalize our findings, this novel method for the synthesis of DHPMs was applied to a number of substituted aromatic aldehyde compounds. The experimental results are summarized in TABLE 1. Aromatic aldehydes (containing either electron withdrawing or

## Full Paper

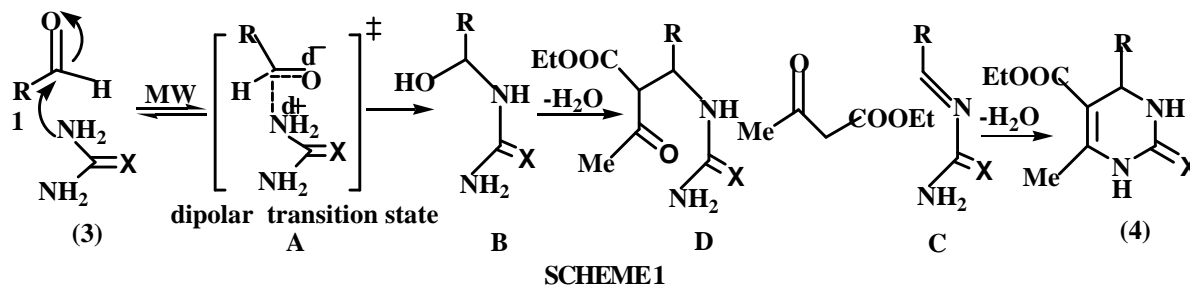


TABLE 1 : Microwave assisted synthesis of dihydropyrimidinones (4)

Sl.no	Product <sup>a</sup>	R	X	Power(W)	Time(min)	Yield(%) <sup>b</sup>	Mp (°C) <sup>c</sup>	
							Found	Reported[ref]
1	4a	C <sub>6</sub> H <sub>5</sub>	O	300	6	42	203	202-204 <sup>[9a]</sup>
2	4a	C <sub>6</sub> H <sub>5</sub>	O	600	5	98	203	202-204
3	4b	4-O <sub>2</sub> N-C <sub>6</sub> H <sub>4</sub>	O	600	6	94	209-210	208-209 <sup>[9a]</sup>
4	4c	4-Cl-C <sub>6</sub> H <sub>4</sub>	O	600	5	93	210-213	213-215 <sup>[9a]</sup>
5	4d	4-OMe-C <sub>6</sub> H <sub>4</sub>	O	600	5	90	204-206	201-203 <sup>[9a]</sup>
6	4e	2-O <sub>2</sub> N-C <sub>6</sub> H <sub>4</sub>	O	600	5	85	220	218-220 <sup>[9b]</sup>
7	4f	3,4,5-(OMe) <sub>3</sub> -C <sub>6</sub> H <sub>2</sub>	O	600	13	86	217-218	216-218 <sup>[9c]</sup>
8	4g	3-O <sub>2</sub> N-C <sub>6</sub> H <sub>4</sub>	O	600	6	97	227-228	226-227 <sup>[9d]</sup>
9	4h	2-OH C <sub>6</sub> H <sub>4</sub>	O	900	6	85	202-203	201-203 <sup>[9a]</sup>
10	4i	4-Me C <sub>6</sub> H <sub>4</sub>	O	600	10	98	169-171	168-170 <sup>[9c]</sup>
11	4j	Cinnamyl-	O	600	7	96	242-243	241-242 <sup>[9c]</sup>
12	4k	Furyl-	O	600	7	80	203-204	204.5-205 <sup>[9a]</sup>
13	4l	C <sub>6</sub> H <sub>5</sub>	S	450	2	98	205-207	205-206 <sup>[9e]</sup>
14	4m	4-O <sub>2</sub> N-C <sub>6</sub> H <sub>4</sub>	S	450	12	97	108-110	109-111 <sup>[9f]</sup>
15	4n	4-Cl-C <sub>6</sub> H <sub>4</sub>	S	450	10	87	193-195	192-194 <sup>[9f]</sup>
16	4o	4-OMe-C <sub>6</sub> H <sub>4</sub>	S	180	10	-	-	-
17	4o	4-OMe-C <sub>6</sub> H <sub>4</sub>	S	450	5	85	151-153	152-154 <sup>[9e]</sup>
18	4p	Furyl-	S	180	6	-	-	-
19	4p	Furyl-	S	300	10	90	216-217	215-216 <sup>[9f]</sup>
20	4q	3-O <sub>2</sub> N-C <sub>6</sub> H <sub>4</sub>	S	600	5	93	205-206	206-207 <sup>[6e]</sup>
21	4r	4-Me C <sub>6</sub> H <sub>4</sub>	S	900	7	95	193-194	192-194 <sup>[9f]</sup>
22	4s	3,4,5-(OMe) <sub>3</sub> -C <sub>6</sub> H <sub>2</sub>	S	900	7	96	203-205	202-204 <sup>[9g]</sup>

<sup>a</sup>All products were characterized by FT-IR, <sup>1</sup>HNMR, CHN analyzer and also their melting points with that of previous literatures,

<sup>b</sup>Isolated yield, <sup>c</sup> Melting points are uncorrected

electron donating substituents) afforded high yields of products in high purity (entry 3-10). Acid sensitive aldehyde such as cinnamaldehyde and furaldehyde also worked well without any side product, which is normally observed in the presence of protic acids or Lewis acid due to their polymerization under acidic conditions (entry 11 and 12). In addition, this method efficiently worked in presence of thiourea to provide the corresponding 3,4-dihydropyrimidin-2(1H)-thiones (entry 13-22) which are also of interest with regard to their biological activities. 4-Methoxy benzaldehyde (entry 16) and furaldehyde (entry 18) did not participate in the reaction under 180 W power of MW, instead we get the starting compounds back.

The driving energy by microwave irradiation results

from material wave interactions leading to thermal and specific effects. Loupy et al.<sup>[1a]</sup> already reviewed the effect of microwave irradiation on polarity of reaction systems. Effect of MWI will be more in case of polar mechanism. As far as mechanism<sup>9c</sup> of the reaction is concerned, we believe the reaction proceeds with an increase of polarity via the formation of dipolar transition state. Accelerated by specific microwave effect (SCHEME 2). Consequently in solvent-free condition, favorable outcomes are expected. This further reacts with the ethyl acetoacetate to give the cyclized product with the elimination of water.

## CONCLUSION

The main advantages of this methodology are (a) simple work up procedure using water as the solvent (b) shorter reaction time (c) higher yields (d) solventless and catalyst-free condition. In summary, the present procedure provides an efficient and improved modification of the Biginelli reaction in green synthesis.

## ACKNOWLEDGMENT

The author thanks Council of Scientific and Industrial Research for granting a Research Project(No. 01(2067)/06/EMR-II).

## REFERENCES

- [1] (a) L.Perreux, A.Loupy; *Tetrahedron*, **57**, 9199 (2001).  
 (b) P.Lidstrom, J.Tierney, B.Wathey, J.Westman; *Tetrahedron*, **57**, 9225 (2001).  
 (c) A.Stadler, C.O.Kappe; *J.Chem.Soc.Perkin.Trans* **2**, 1363 (2000).
- [2] C.O.Kappe; *Tetrahedron*, **49**, 6937-6963 (1993).
- [3] (a) G.C.Rovnyak, S.D.Kimball, B.Beyer, G.Cucinotta, J.D.DiMarco, J.Gougoutas, A.Hedberg, M.Malley, J.P.McCarthy, R.Zhang, S.Moreland; *J.Med.Chem.*, **38**, 119 (1995).  
 (b) K.S.Atwal, G.C.Rovnyak, S.D.Kimball, D.M.Floyd, S.Moreland, B.N.Swanson, J.Z.Gougoutas, J.Schwartz, K.M.Smillie, M.F.Malley; *J.Med.Chem.*, **33**, 1510 (1990).  
 (c) H.Cho, M.Ueda., K.Shima, A.Mizuno, M.Hayashimatsu, Y.Ohnaka, Y.Takeuchi, M.Hamaguchi, K.Aisaka, T.Hidaka, M.Kawai, M.Takeda., T.Ishihara, K.Funahashi, F.Sato, M.Morita, T.Noguchi; *J.Med.Chem.*, **32**, 2399 (1989).  
 (d) C.O.Kappe; *Eur.J.Med.Chem.*, **35**, 1043-1052 (2000).
- [4] P.Biginelli, *Gazz Chim Ital* **23**, 360 (1893).
- [5] (a) M.M.Aghayan, M.Bolourtchian, M.Hosseini; *Synthetic Communications*, **34**, 3335 (2004).  
 (b) A.Mobinikhaledi, N.Foroughifar, H.F.Jirandehi, Phosphorus, Sulfur and Silicon; **179**, 2259 (2004).  
 (c) J.J.V.Eynde, N.Hecq, O.Kataeva, C.O.Kappe, *Tetrahedron*, **57**, 1785 (2001).  
 (d) M.S.Manhas, S.N.Ganguly, A.Mukherjee, A.K.Jain A.K.Bose; *Tetrahedron Letter*, **47**, 2423 (2006).
- [6] (a) X.Zhang, Y.Li, C.Liu, J.Wang, *J.Mol.Catal A: Chemical*; **253**, 207 (2006).  
 (b) J.Azizian, A.A.Mohammadi, A.R.Karimi., M.R.Mohammadizadeh, *Appl.Catal A: General*, **300**, 85 (2006).  
 (c) M.A.Chari, K.Syamasundar, *J.Mol.Cat.A: Chemical*, **221**, 137 (2004).  
 (d) P.Salehi, M.Dabiri M.A.Zolfigol, M.A.B.Fard; *Tetrahedron Lett.*, **44**, 2889(2003).  
 (e) A.Shaabani, A.Bazgir, F.Teimouri; *Tetrahedron Lett.*, **44**, 857 (2003).  
 (f) S.Tu, F.Fang, C.Miao, H.Jiang, Y.Feng, D.Shi, X.Wang; *Tetrahedron Lett.*, **44**, 6153 (2003).  
 (g) H.Lin, J.Ding, X.Chen; Z.Zhang; *Molecules.*, **5**, 1240 (2000).
- [7] (a) J.Peng, Y.Deng; *Tetrahedron Lett.*, **42**, 5917 (2001).  
 (d) M.Xia, Y.G.Wang; *Tetrahedron Lett.*, **43**, 7703 (2002).
- [8] B.C.Ranu, A.Hajra, S.S.Dey; *Org.Proc.Res.Dev.*, **6**, 817 (2002).
- [9] (a) J.Lu, Y.Bai; *Synthesis.*, **4**, 466 (2002).  
 (b) C.O.Kappe, U.G.Wagner; *Heterocycles.*, **29**, 761 (1989).  
 (c) J.S.Yadav, B.V.S.Reddy, K.B.Reddy, K.S.Raj, A.R.Prasad; *J.Chem.Soc.Perkin Trans.*, **1**, 1939 (2001).  
 (d) C.O.Kappe, D.Kumar, R.S.Varma; *Synthesis.*, 1799 (1999).  
 (e) M.M.Heravi, K.Bakhtiari, F.F.Bamoharram; *Catalysis Communications*, **7**, 373 (2006).  
 (f) N.Y.Fu, Y.F.Yuan, Z.Cao, S.W.Wang, J.T.Wang, C.Peppe; *Tetrahedron*, **58**, 4801 (2002).  
 (g) A.R.Gholap, K.Venkatesan T.Daniel, R.J.Lahoti, K.V.Srinivasan; *Green Chemistry*, **6**, 147 (2004).